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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,252	02/27/2007	Freda D. Miller	50037/003003	3359

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EXAMINER	
BARNHART, LORA ELIZABETH	

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
06/29/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/587,252	MILLER ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-58 and 60-71* is/are pending in the application.

4a) Of the above claim(s) *42-52,60 and 64-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53-58,61-63 and 69-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/20/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 4/20/10 to claims 53, 55, 57, 58, and 60 have been entered. Claims 1-41 and 59 have been canceled. Claims 69-71 have been added. Claims 42-58 and 60-71 remain pending in the current application, of which claims 53-58, 61-63, and 69-71 are being considered on their merits. Claims 42-52, 60, and 64-68 remain withdrawn from consideration at this time. References not included with this Office action can be found in a prior action. Any rejections of record not particularly addressed below are withdrawn in light of the claim amendments and applicant's comments.

Election/Restrictions

Applicant's election without traverse of the species "nestin," "p75 NTR," and "accidental injury" in the 7/16/09 reply is still in effect over the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 53-58, 61-63, and 69-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 53, from which all other claims under examination depend, has been amended to require that the administered stem cells or progeny thereof do not express measurable levels of keratin 15 using various methodologies. However, the as-filed specification taken in view of the art provides no basis for this new limitation.

The specification describes a population of cultured multipotent skin-derived precursor cells isolated from mammalian skin (SKPs; see page 1, lines 22-26; and page 17, lines 26-30). The specification does not include any detailed protocol for preparing these cells, referring instead to two WIPO publications. See page 2, lines 2-8; page 4, lines 19-21; and page 5, lines 10-19. Example 1 of the specification characterizes SKPs as expressing nestin and fibronectin, but not p75NTR. See page 18, lines 16-20. However, Example 1 is silent as to whether SKPs express keratin 15. As basis for the introduction of this limitation, applicant refers to page 25, line 10. This passage is within Example 4, which does not characterize SKPs themselves but rather traces the progeny of neural crest stem cells (NCSCs) throughout developing skin. In Example 4, NCSCs and their progeny were tagged in transgenic mice with a β-galactosidase marker. See page 25, lines 2-4. Example 4 indicates that at postnatal day 5 (P5), the β-galactosidase-positive cells did not express keratin 15. See page 25, lines 7-10. However, Example 4 indicates that SKPs cannot be isolated from papillae until postnatal day 9. See page 25, lines 21-23. SKPs themselves were analyzed at page 26, lines 1-14, but all that is concluded is that SKPs are NCSC progeny. It is not clear

that the experiment at page 25, lines 2-20, describes SKPs, since it actually appears to characterize the properties of cells in the developing follicle well before those cells yield SKPs.

Furthermore, there is no support in the specification for claiming a cell that does not express keratin 15 according to all of the methods recited in claim 53. Example 4 appears to be limited to immunohistochemical analyses, which are relatively insensitive relative to at least one of the other methods in the claim. For example, RT-PCR is 100 times more sensitive than immunohistochemistry, since it can detect one cell out of a million. See Reintgen, 2000, U.S. Patent 6,153,388, at column 6, lines 29-34 (attached as reference A). In other words, even if SKPs were negative for keratin 15 according to histological analyses (which the examiner does not concede), Reintgen's teachings provide a reasonable basis for concluding that a more sensitive assay might identify expression levels too low for histochemical analysis to observe. The RT-PCR analysis of SKPs at pages 29-30 is silent as to SKPs' expression of keratin 15.

This rejection would be overcome by a substantive evidentiary showing that RT-PCR indicates that SKPs do not express keratin 15.

Claim Rejections - 35 USC §§ 102 and 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 53-58, 61, 63, and 69 are/remain rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Tankovich et al. (2000, U.S. Patent 6,050,990) taken in light of Li et al. (2003, U.S. Patent Application Publication 2003/0077823) and Toma et al. (2001, WO 01/53461; on 7/16/09 IDS).

Tankovich teaches isolating skin comprising dermal papillae from a patient's own head; separating stem cells from said skin; cloning the cells (i.e., culturing them to homogeneity); and grafting the cells into incision on a desired area on said patient's own head (column 56, line 15, through column 57, line 22). The incisions made at the recipient site are reasonably interpreted as "damaged skin."

Tankovich does not explicitly teach that dermal papilla and bulge area stem cells express nestin but not p75 NTR or keratin 15. However, Li teaches a population of stem cells in hair follicles that expresses nestin and regenerates skin (paragraphs 22, 30, and 49) and Toma teaches a population of stem cells isolated from skin that express nestin but not p75 NTR (page 18, line 20, through page 19, line 19). The reasonable inference from the combined teachings is that the stem cells of Tankovich express nestin but not p75 NTR.

The Patent and Trademark Office is not equipped to conduct experimentation in order to determine whether or not applicants' nestin- and fibronectin-positive, p75 NTR- and keratin 15-negative stem cell differs, and if so to what extent, from the dermal papilla cells discussed in Tankovich. The cell of Tankovich is isolated from dermal papilla, as is applicants' cell; Li teaches that stem cells isolated from hair follicle express nestin; and Toma teaches a population of skin stem cells that express nestin and fibronectin, but not p75 NTR. The cited art taken as a whole demonstrates a reasonable probability that the cell of Tankovich is either identical or sufficiently similar to the cell in the claimed method that whatever differences exist are not patentably significant. Therefore, the burden of establishing novelty or unobviousness by objective evidence is shifted to applicants.

Merely because a characteristic of a known cell is not disclosed in a reference does not make that cell patentable. Applicants' stem cell possesses inherent characteristics which might not be displayed in the tests used in Tankovich. Clear evidence that the dermal papilla stem cells of the cited prior art does not possess a

critical characteristic (e.g., expression of nestin and fibronectin or lack of expression of p75NTR or keratin 15) that is possessed by the cell in the claimed method would advance prosecution and might permit allowance of claims to applicants' method.

Regarding the rejections of record, applicant alleges that Tankovich's patient is not "in need of" skin regeneration because they are undergoing hair transplantation. See reply, pages 8-9. Applicant alleges that Tankovich's cells are "bulge area cells" that are different from the cells of the instant claims. See reply, page 9. Applicant alleges that Tankovich does not teach "multipotent stem cells derived from the [dermal papilla]." See reply, page 9. Applicant alleges that dermal papilla cells lose the ability to induce hair follicle formation when cultured. See reply, pages 9-10. These arguments have been fully considered, but they are not persuasive.

First, Tankovich's patient has been subjected to an incision in the skin. Any individual with a cut in the skin is "in need of" skin regeneration. The claims do not require that any particular amount of skin is regenerated in the method. Healing Tankovich's cut, even with skin cells that contain develop follicles, constitutes regeneration of skin. One cannot regenerate hair without affecting the skin; Tankovich's method requires applying stem cells to an incision, then allowing them to differentiate into hair follicle-bearing skin cells. Follicles cannot exist without surrounding skin.

Applicant has misinterpreted the teachings of Tankovich. Tankovich teaches, "Undifferentiated stem cells are separated out from the mid derm bulge area of hair papilla in the tissue samples . . .The separated stem cells are then cloned by culturing them in an appropriate growth medium." See column 56, lines 48-53. Tankovich

discards the bulge area cells and continues the protocol with the stem cells, first differentiating them in culture and then applying them to the skin surface. See column 57, lines 17-22. The examiner points out that claim 53 does not actually require administering stem cells; the claim requires administering stem cells "or progeny thereof." Tankovich's differentiated cells are "progeny" of the stem cells obtained in column 56.

The examiner has considered the Rendl reference, but it is not persuasive of error. Applicants' exemplified method is that described in the Toma reference (see page 2, lines 2-8; page 4, lines 19-21; page 5, lines 10-19; and page 26, lines 20-21), and it requires culturing SKPs in DMEM supplemented with growth factors. See page 26, lines 20-30. Indeed, the exemplified method refers to a "proliferation medium" and passaging the cells; therefore, Toma's method (which was employed by applicants) requires culturing SKPs. The Rendl reference and accompanying argument appear to indicate that the cells yielded by applicants' method at page 26 have lost their ability to induce hair follicle formation. However, the importance of this fact is queried, since the claims are drawn to a method of regenerating skin, not forming hair follicles.

Tankovich and Toma both teach methods in which stem cells are obtained from skin samples, then cultured. Applicant teaches a method in which stem cells are obtained from skin samples, then cultured. Tankovich teaches applying these stem cells to wounded skin; the instant claims require administering stem cells to a mammal such that the cells regenerate skin. The wound of Tankovich is only one species of "needs" for regenerated skin.

Claims 53-58, 61-63, and 69-71 are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over Tankovich et al. (2000, U.S. Patent 6,050,990) taken in view of Li et al. (2003, U.S. Patent Application Publication 2003/0077823) and Toma et al. (2001, WO 01/53461; on 7/16/09 IDS).

Tankovich teaches isolating skin comprising dermal papillae from a patient's own head; separating stem cells from said skin; cloning the cells (i.e., culturing them to homogeneity); and grafting the cells into incision on a desired area on said patient's own head (column 56, line 15, through column 57, line 22).

Tankovich does not teach isolating cells that express nestin and fibronectin, but not p75NTR or keratin 15. Tankovich does not teach treating a mammal whose skin is damaged accidentally.

Li teaches a population of nestin-expressing stem cells in hair follicles that can regenerate skin (paragraphs 22, 30, and 49).

Toma teaches a population of stem cells isolated from skin that express nestin and fibronectin, but not p75NTR (page 18, line 20, through page 19, line 19).

A person of ordinary skill in the art would have had a reasonable expectation of success in isolating stem cells from hair follicles that express nestin and fibronectin but not p75NTR or keratin 15 and are capable of regenerating skin because Tankovich teaches that stem cells from hair follicles can regenerate skin and hair; Li teaches that stem cells from hair follicles express nestin and can regenerate skin; and Toma teaches a population of stem cells isolated from skin that express nestin and fibronectin but not

p75NTR. The reasonable inference from the combined teachings is that the stem cells of Tankovich express nestin and fibronectin but not p75NTR or keratin 15.

The manner in which the skin was damaged would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Tankovich's method applies to sealing incisions made in skin with new, hair-growing skin. An incision made deliberately is identical to one made accidentally. A holding of obviousness over the cited claims is therefore clearly required.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to transplant multipotent stem cells isolated from dermal papilla or hair follicles into damaged skin because Tankovich's method regenerates hair-growing skin in an incision (i.e., damage to the skin). It would have been further obvious that the stem cells employed in Tankovich's method express nestin but not p75 NTR because Li teaches that stem cells from hair follicle regenerate skin and regenerate nestin and Toma teaches a population of multipotent stem cells isolated from skin that express nestin and fibronectin but not p75NTR or keratin 15.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicant relies in part on arguments set forth against the above rejection; therefore, these arguments are unpersuasive as they pertain to this rejection for the same reasons. See reply, pages 11-12.

No claims are allowed. No claims are free of the art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is (571)272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651